Respectfully, Applicants assert that Martins fails to expressly teach each and every element of the claimed invention. Claim 1 relates to a method of inducing and/or sustaining an immunoligical CTL response in a mammal. The method includes delivering an antigen to the mammal at a level sufficient to induce an immunologic CTL response in the mammal and maintaining the level of the antigen in the mammal's lymphatic system over time sufficient to maintain the immunologic CTL response.

Martins does not expressly disclose inducing and/or sustaining a CTL response. Martins discloses a method for potentiating an immune response, particularly an antibody response, by continuous administration of a combination of antigen and immunopotentiator. *See* column 3, lines 41-48. Martins mentions "cell-mediated immunity," which is an exceedingly broad and vague term. *See* column 3, lines 55-57.

Cell-mediated immunity, as used in the art, can refer to innate and adaptive immune systems involving cells such as monocytes and natural killer (NK) cells, both of which can be activated by the immunopotentiators of Martins. Cell-mediated immunity can also refer to antibody-dependent cellular cytotoxicity, in which monocytes and NK cells augment their innate activity by using antibodies as antigen receptors. Further, cell mediated immunity can refer to the mediators of the adaptive cellular response, helper T-cells and cytotoxic T Lymphocytes, for example.

In its usage of the term "cell-mediated immunity," Martins mentions potentiating the immune system by acting directly on macrophages to increase their activity, by increasing T-cell response, by increasing B-cell response, by increasing NK-cell response, and by increasing complement activity. *See* column 4, lines 54-60. However, Martins does not disclose inducing and/or sustaining an immunological CTL response in a mammal by the method of claim 1. Indeed, at the time of the filing of the Martins patent application, the induction of CTL responses was poorly understood. Thus, Martins failed to disclose each and every feature of claim 1.

During the interview on January 24, 2002, the Examiner raised the issue of possible inherent anticipation. To inherently anticipate, the reference "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill." *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) and M.P.E.P. § 2112. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result for a

given set of circumstances is not sufficient." *Continental Can Co.* at 1269 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)) and M.P.E.P. § 2112.

Martins fails to inherently teach each and every feature of the claims. Martins does not disclose a method that would necessarily and always induce and/or sustain an immunological CTL response in a mammal commensurate with claim 1. In support, please see the accompanying Declaration of David C. Diamond under 37 C.F.R. § 1.132. Therefore, Martins does not inherently teach each and every feature of the claims.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 102, and allowance of the pending claims.

Discussion of Rejection Under 35 U.S.C. § 103

The Office Action rejected Claims 2, 3, 5-6, 11-13, 15-16, and 20-21 under 35 U.S.C. § 103(a) as being unpatentable over Martins as applied to Claims 1 and 4 under § 102(b) in view of Kundig (*Science*, 268:1343-1347). Claims 17-19, 41-42, and 53-54 were rejected under § 103(a) as being upatentable over Martins, as applied to Claims 4, 39 and 48 under § 102(b), and further in view of Falo, Jr., et al. ("Falo Jr.") (U.S. Patent No. 5,951,975). Further, the Office Action rejected Claims 40 and 60 under § 103(a) as being unpatentable over Martins as applied to Claims 39 and 59 under § 102(b), and further in view of Eberlein et al. ("Eberlein") (U.S. Patent No. 5,550,214).

To establish a *prima facie* case of obviousness, a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As discussed above, Martins fails to teach each and every element of the claims. Martins, even in view of the other cited references, fails to teach or suggest all of the features of the claims. Claim 1 is not obvious over Martins, even in view of Kundig. According to standard models of the immune system, a naïve T-cell that encounters a fibroblast should not be immunized, but instead should be anergized (conditioned to fail to respond) to any antigen presented by the fibroblast. *See Kundig* at page 1343. Kundig reports that if that encounter

between the fibroblast and antigen takes place in a lymphoid environment, the fibroblast can serve as an APC, thus leading to immunization. *See Kundig* at pages 1343, 1345. Kundig shows that the route of injection determines the efficiency of this type of immunization. *See Kundig* at pages 1344-1345. Subcutaneous (s.c.), intraperitoneal (i.p.), and intrasplenic (i.spl.) injections require progressively smaller doses. *See id.* However, Kundig does not teach maintaining a CTL response, an aspect of all claims of the present invention. Thus, Martins in view of Kundig still fails to render the present invention obvious. Falo Jr. and Eberlein do not disclose the features of the claims lacked by Martins and/or Kundig.

The understanding in the art of the various requirements to induce responses by the various arms of the immune system, and the requirements for inducing a CTL response in particular, were vastly different in the late 1990s when the present application was created than in 1982 when Martins was written. From the viewpoint of the person of ordinary skill in the art at the time the invention was made, Martins is essentially a method of improving antibody response, and provides no particular teaching useful to the generation of a CTL response. Thus it would be viewed as largely irrelevant and there would be a lack of motivation to combine Martins with any other reference to create a method to induce and/or sustain a CTL response.

Accordingly, for all of the foregoing reasons, none of the claims is obvious under § 103(a). Therefore, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103, and allowance of all of the pending claims.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. In light of the above remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 28 Feb 2002

By: _____

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